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ART UNIT	PAPER NUMBER
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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire _____ ~~month(s), or~~ (thirty days), ~~whichever is longer,~~ from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-20 is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☐ Claim(s) _____ is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims 1-20 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

– SEE OFFICE ACTION ON THE FOLLOWING PAGES –

* U.S. GPO: 1996-409-290/40029

DETAILED ACTION

Election/Restriction

1. Applicant's election of Group I in Paper No. 6 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-20 have been canceled in the instant application. New claims 21-39 have been added which correspond to the claims of Group I which have been elected for examination.

Sequence Compliance

2. 37 CFR 1.821(a) defines the amino acid sequences which must be represented in the Sequence Listing as an unbranched sequence of four or more amino acids. Page 6, line 24 contains an amino acid sequence which is not represented by a SEQ ID NO. Correction is required. In order to comply with the Sequence Rules, Applicant must submit a substitute computer readable form of the Sequence Listing, a substitute paper copy of the Sequence Listing, an amendment directing its entry into the specification, and a statement that the computer readable form and the paper copy are the same and include no new matter.

3. The specification is also not in compliance with 37 C.F.R. § 1.822(e) which requires the exclusive use of specific three letter abbreviations to depict the amino acids in an amino acid sequence whenever such a sequence is presented in a patent application. The above mentioned amino acid sequence uses single letter code instead of the required three letter code. The correction of all instances of single letter code to three letter code is required. See M.P.E.P. 2422.02.

Specification

4. Applicant is reminded of the proper content of an abstract of the disclosure.

A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure. The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art.

5. The abstract of the disclosure is objected to because it is not directed to the claimed invention. Correction is required. See MPEP § 608.01(b).

6. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed (i.e. nucleic acids encoding human vascular endothelial growth factor 3 [VEGF-3]).

Claim Objections

7. Claims 31-33 are objected to because of the following informalities:

Claims 31, 32 and 33 recite "expressing from the host cell . . . the polypeptide encoded . . ." It is suggested that these claims be amended to read approximately as follows: "culturing the host cell of claim x under conditions suitable to produce the polypeptide encoded by said DNA", thereby employing more conventional claim language. Appropriate correction is required.

Double Patenting

8. Claim 26 rejected under 35 U.S.C. 101 as being a substantial duplicate of claim 24. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to reject the other as being a substantial duplicate of the allowed claim. Claim 26 is an exact duplicate of claim 24. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 112

9. Claims 31-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling methods of making a polypeptide by expressing the DNA which encodes the polypeptide of SEQ ID NO:2, does not reasonably provide enablement for methods of making a polypeptide by expressing polynucleotides

having 95% identity to polynucleotides which encode a polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims (31-33) ultimately depend on claim 21. Claim 21 is directed to polynucleotides which have at least 95% identity to (1) a polynucleotide encoding a polypeptide and (2) the complement of a polynucleotide encoding a polypeptide. First, the polynucleotide sequence of (1) and (2) include degenerate sequence. A polynucleotide having 95% identity to a degenerate sequence encoding a polypeptide would not necessarily encode the protein anymore. Claims to polynucleotides having a percent identity are typically designed as probe claims or for obtaining claims to allelic variants of the naturally occurring DNA. However, as the current claims are drafted, the claimed polynucleotides may bear no resemblance to the naturally occurring DNA encoding the polypeptide. In Ex parte Forman, 230 USPQ 546 (Bd. Pat. Appls, and Interf. 1986), the Board considered the issue of enablement in molecular biology. The Board held that the following factors should be considered to determine whether the claimed invention would require of the skilled artisan undue experimentation:

(a) quantity of experimentation necessary
(b) amount of direction or guidance presented
(c) presence or absence of working examples
(d) nature of the invention
(e) state of the prior art

(f) relative skill of those in the art
(g) predictability or unpredictability of the art and
(h) breadth of the claims.

In the instant case, the claims broadly encompass any DNA having at least 95% identity to a DNA encoding a polypeptide (comprising a specific amino acid sequence). It would require undue experimentation by one of ordinary skill in the art to determine which of the multitude of DNA's encompassed by the instant claims that meet the structural limitations (being 95% identical to a DNA) would also meet the functional limitations of the claims (encoding a polypeptide). The specification provides a single example of a DNA which encodes a polypeptide (SEQ ID NO:1) but fails to describe even a single other working example. The instant claims encompass variants, analogs, and derivatives, yet the specification provides no guidance or examples as how the DNA could be modified and still encode a polypeptide with the activity of the polypeptide of SEQ ID NO:2. The nature of the invention is novel in that the DNA and polynucleotide of SEQ ID NO:1 and 2 are not known in the prior art, therefore, no guidance can be obtained from the prior art. The skill in the art may be high, but it is well known and established that the art of mutating proteins and retaining biological activity is unpredictable. Therefore, the experimentation required to practice the claimed invention would be considered undue, absent clear and convincing evidence to the contrary.

If the claims are amended to claim methods of making a polypeptide by expressing the DNA which encodes the polypeptide of SEQ ID NO:2, this rejection would be overcome. However, if claims to fragments, analogs, or derivatives encoding a polypeptide are included, these claims will be rejected for lack of enablement for the reasons given above.

10. Claims 37-39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification and claims have been amended to recite ATCC Deposit No. 97166 in the amendment filed 21 October 1996. However, this deposit number was not present in the specification as originally filed and Applicant has provided no basis for its insertion. In the absence of information associating this deposit number with a specific biological material disclosed in the specification, this is deemed to constitute new matter.

It is noted that the specification fails to adequately describe the clone deposited to the ATCC. The specification states that the clone contains cDNA encoding the mature polypeptide. However, it is presumed that the clone is contained in some type of vector because this is routine in the art for deposited sequence, bu the specification

does not describe this. Even if the deposit is perfected in accordance with MPEP 2402 as set forth below, this may not overcome the inadequate description in the specification.

The enablement of the claims requires availability of the ATCC deposit. This determination has been made because the sequences of the clone have not been fully disclosed nor been shown to be publicly known and freely available. Accordingly, it is deemed that a deposit should have been made in accordance with MPEP 2402. In order to certify that the deposit meets the criteria set forth in MPEP 2402, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number. Applicant is advised that the Patent Office accepts Budapest approved deposits, as long as assurance is provided that the deposited plasmids will be made irrevocably available with no restrictions upon issuance of a patent.

11. Claim 36 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 36 is unclear and indefinite because of the language "comprising the nucleotides of the sequence of SEQ ID NO:1". This language appears to imply that the polynucleotide of the claim could comprise the nucleotides of the SEQ ID NO in any

order, which would read on a scrambled DNA which would not be useful for hybridization, probing, or for expressing the protein. The claim could be amended to "having the sequence of SEQ ID NO:1" or "comprising the sequence of SEQ ID NO:1" or "consisting of the sequence of SEQ ID NO:1", etc. However, as the claim presently stands, it is unclear and indefinite what polynucleotide is being claimed. (Care should be taken not to create a duplicate claim when the claim is amended.)

Allowable Subject Matter

12. Claims 21-25, 27-30, and 34-35 are allowed over the prior art.

13. The following is a statement of reasons for the indication of allowable subject matter: The specification states on page 20, line 9-12 that "VEGF3 may be employed for *in vitro* culturing of vascular endothelial cells, where it is added to the conditional medium in a concentration from 10 pg/ml to 10 ng/ml." The record does not establish that this statement is incorrect; therefore, this positive assertion is deemed to be an enabled use for the protein and by extension and enabled use for the claimed polynucleotides, expression vectors, host cells, and processes for producing the polypeptide. The claimed polynucleotides, expression vectors, host cells, and processes can be used to make the protein. No other uses set forth in the specification for the

claimed polynucleotides, expression vectors, host cells, and processes for producing the polypeptide are deemed to be enabled for at least the following reasons.

The specification discloses a DNA and deduced amino acid sequence in Figure 1. The specification identifies the encoded protein as a vascular endothelial growth factor, VEGF3, based upon some sequence similarity to proteins known to have growth factor activity (PDGF-A, PDGF-B, and VEGF). The specification provides no evidence that the disclosed protein has this activity. Based upon the limited similarity to these known protein, it cannot be predicted with any expectation of success that the full length protein has this activity, much less fragments, analogues and derivatives thereof. For example, the TGF-β superfamily includes proteins with some sequence similarity (many higher than that of the instant application), but widely divergent activity. These proteins include TGF-β1, 2, and 3; bone morphogenetic proteins (BMPs), activins, inhibins, and dpp (involved in dorsal-ventral specification in early embryogenesis). Likewise, VEGF and PDGF have very different activities even though the possess some sequence similarity. (See Tischer et al., page 1205, second complete paragraph.) Thus, even if the disclosed DNA sequence encodes a protein that is in fact determined to be a member of a PDGF/VEGF superfamily, it could not be predicted what activity it would have. The metes and bounds of "VEGF3 activity" as recited in the specification cannot be determined. The specification does not appear to provide any activity assays. The

specification ans prior art of record do not establish that the protein encoded by the disclosed polynucleotides possesses any biological activity.

The specification states that the nucleic acid sequence may be used to make proteins to be used in pharmaceutical compositions in methods of treatment. However, without knowing the activity the protein possesses, one would not know which diseases would be appropriately treated. Various uses of VEGF3 have been disclosed (beginning on page 18) which include stimulation of transplanted tissue growth, revascularization, induction of bone growth, promotion of endothelialization, for minimizing rejection of transplanted material, repair of myocardial tissue, etc. These uses are not enabled because the specification does not teach one of ordinary skill in the art how to use the protein in the manner disclosed. Even if the protein disclosed in the instant application has the activity necessary to accomplish all of the therapies recited in the specification, the specification fails to disclose how VEGF3 could be used to treat all of these various problems. There is no guidance or teaching or examples which would enable one of ordinary skill in the art to administer the protein of the instant application and effectively treat all of these various conditions (i.e. no dosages, methods of administration, dosing schedules, etc.). It would require undue experimentation by one of ordinary skill in the art to use VEGF3 in the manner suggested by the instant specification. Gene therapy uses are not enabled for the same reasons.

Another stated use of the nucleic acid sequences is for human chromosome identification by preparing PCR primers. (See page 30.) This use does not fulfill Applicant's burden of telling how to use the claimed polynucleotide fragments, analogues, and derivatives; polynucleotide sequences that are degenerate due to the genetic code (i.e. not the actual DNA sequence isolated even though they encode the same protein), RNA, hybridizing sequences, vectors, host cells, processes for producing the cell, and methods of producing the protein in a patentable manner. In addition, the specification does not demonstrate that the DNA sequence of Figure 1 or primers can be used to uniquely identify a human chromosome. Multiple copies of this gene or related genes could occur on different chromosomes. Alternatively, the DNA of Figure 1 or primers could occur in different exons. It is noted that the genomic sequence is not disclosed in the specification and that the method for identifying chromosomes requires computer analysis of the genomic DNA. The prior art of record and specification do not establish a link between this gene and any known human disease.

Page 6 defines "polynucleotide encoding a polypeptide" to include non-coding sequences. Such a definition is repugnant to those of ordinary skill in the art. A polynucleotide encoding a polypeptide is generally understood to mean only those portions encoding amino acids but not the 5' and 3' untranslated regions. Such regions are present in Figure 1. In view of Applicant's definition, claim 37, for example, may

be considered to encompass the entire sequence of ATCC 97166. (See above rejection with respect to the deposit.)

14. In order to ensure full consideration of any amendments, affidavits or declarations, or other documents as evidence of patentability, such documents **must** be submitted in response to this Office action. Submissions after the next Office action, which is intended to be a final action, will be governed by the requirements of 37 CFR 1.116, which will be strictly enforced.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Saoud, Ph.D., whose telephone number is (703) 305-7519. The examiner can normally be reached on Monday to Friday from 8AM to 4PM.

The fax phone number for this Group is (703) 308-0294. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Christine Saoud, Ph.D.
January 29, 1996
CA

DIAN C. JACOBSON
PRIMARY EXAMINER
GROUP 1800